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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,433	12/18/2001	Robert G. Korneluk	07891/018003	3050

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/024,433	Applicant(s) KORNELUK ET AL.	
	Examiner Sumesh Kaushal Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 06/11/03 has been acknowledged.

Claims 1-14 are pending

Claims 5-8 are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 5-8 in Paper No. 5 is acknowledged.

Claims 1-4 and 9-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses a method for identifying compounds that modulates TIAP biological activity by contacting a TAIP polypeptide (testes-specific XIAP homologue, obtained from any and all organisms) with a candidate compound and determining the ability of the compound to interact with the TIAP polypeptide, wherein the TIAP polypeptide (as claimed) is substantially identical to human TIAP (SEQ ID NO:2) and has 85% or 90% sequence identity to SEQ ID NO:2. At best the specification discloses the amino acid sequences of SEQ ID NO:2, which encodes the human TIAP polypeptide. Furthermore the specification disclosed that by **"substantially identical"** is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids. (spec. page 12, lines 12-20). Therefore the invention as claimed encompasses a TIAP-like polypeptide that is only 50% to 95% identical (5-50% non-identical) to human TIAP polypeptide encoding the amino acid of SEQ ID NO:2 over the entire length of 236 amino acids.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol. 66, No. 4, pp. 1099-1100 (see

http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only teaches the amino acid sequences of SEQ ID NO:2, which encodes the human TIAP polypeptide. The specification fails to disclose any variant of SEQ ID NO:2 that has the structural and functional property of TIAP polypeptide explicitly or implicitly as putatively claimed by the applicant.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the amino acid variants (as claimed) has been defined only by a statement of function that broadly encompasses TIAP-like biological activity, which conveyed no distinguishing information about the identity of the claimed amino acid sequence, such as its relevant structural or physical characteristics. The variation as claimed also encompasses the conserved motifs, which are considered germane to the biological activity of a TIAP polypeptide. Given the broadest reasonable interpretation the scope of invention as claimed encompasses an amino acid sequence which is only 50%-95% identical (5%-50% variation) to the amino acid sequences of SEQ ID NO:2 over the entire length. Such a variation would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

3. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying compounds that modulates human TIAP (SEQ ID NO:2) mediated apoptotic activity in-vitro, does not reasonably provide enablement for a method of screening compounds that modulates the biological activity of any and all variants of human TIAP polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

Invention relates to a method of identifying compounds that modulates TIAP-polypeptide biological activity.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a method for identifying compounds that modulates TIAP biological activity by contacting a TAIP-polypeptide obtained from any and all organisms with a candidate compound and determining the ability of the compound to interact with the TIAP polypeptide, wherein the TIAP polypeptide is substantially identical to human TIAP (SEQ ID NO:2) and has 85% or 90% sequence identity to SEQ ID NO:2. At best the specification discloses the amino acid sequences of SEQ ID NO:2, which encodes the human TIAP polypeptide. Furthermore the specification disclosed that by **"substantially identical"** is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably

35 amino acids. (spec. page 12, lines 12-20). Therefore the invention as claimed encompasses a TIAP-like polypeptide that is only 50% to 95% identical to human TIAP polypeptide encoding the amino acid of SEQ ID NO:2, over the entire length of 236 amino acids. At best the specification teaches the evaluation of TIAP mediated apoptosis to screen candidate compounds, wherein the degree of apoptosis in the presence of a candidate compound is compared to the degree of apoptosis in its absence, under equivalent conditions (spec. page 31). Besides the evaluation of the apoptotic activity the specification fails to disclose any other biological activity modulated by the TIAP polypeptide.

State Of Art And Predictability:

The inhibitor of apoptosis proteins (IAP) form a highly conserved gene family that prevents cell death in response to a variety of stimuli. All of the *iap* genes isolated from different species have the common structure termed the baculovirus IAP repeat (BIR) that is present in either two or three copies. Another common feature among IAP proteins is a RING finger domain at the C terminus, the function of which still remains unclear. Proteins containing BIR domains have been identified in a wide range of eukaryotic species, including yeast, nematode, insect and several mammalian species including mice, rats, chickens, pigs, and humans. However, membership in the IAP family of proteins requires both the presence of a BIR domain and the ability to suppress apoptosis. In this regard, many of these BIR-containing proteins are untested with respect to apoptosis suppression. Structure-function studies of IAP family proteins performed to date have uniformly demonstrated a requirement for at least one BIR domain for suppression of apoptosis, although other domains found within some IAPs may also be required under certain circumstances. For example, several of the mammalian, fly, and viral IAPs have a

RING domain located near their carboxyl termini. The necessity for the RING domain for suppression of apoptosis appears to depend on cellular context. Taken together, the domain structure of IAPs suggests that the common unit, the BIR domain, can be linked with a variety of other motifs. These non-BIR motifs presumably either diversify the functions of IAPs or provide ways of regulating individual members or subgroups of the family of IAP proteins. Although all IAP family proteins require at least one BIR domain for their anti-apoptotic function, it should be emphasized that not all BIR-containing proteins are necessarily involved in apoptosis regulation as indicated by the failure of the Ac-IAP protein to suppress apoptosis despite harboring a BIR domain. Furthermore, BIR1 and BIR3 domains of XIAP apparently lack caspase-binding capability, despite their striking amino acid similarity to BIR2 (42% for BIR1; 32% for BIR3). Assuming these results cannot be ascribed to trivial explanations such as misfolding of protein fragments taken out of their normal context of the intact protein, these observations suggest that not all BIR domains are created equal. Thus, it is plausible that even BIR domains within the same protein may have distinct functions see Deveraux et al (Gene & Dev. 13(3): 239-252, 1999).

In the instant case variation as claimed also encompasses the conserved motifs like BIR domains, which are considered germane to the biological activity of a TIAP polypeptide. Given the broadest reasonable interpretation the scope of invention as claimed encompasses an amino acid sequence which is only 50%-95% identical (5%-50% variation) to the amino acid sequences of SEQ ID NO:2 over the entire length of 236 amino acids (see spec page 31). Such a variation would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and

its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Thus considering the scope of invention as claimed it is highly unpredictable that a compound that interacts with a TIAP-like polypeptide (5-50% variation) would not interact with human TIAP. For example, considering the scope of the variation as claimed an antibody raised against an epitope found in the human TIAP would not bind to a TIAP-like polypeptide, which lacks the required amino acid sequences. In addition any change in BIR domain would abolish the TIAP specific apoptotic activity, which would not enable one skill in the art to identify compounds that modulates TIAP-specific apoptotic activity.

Quantity Of Experimentation Required:

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case screening of any and all natural and non-natural variants, wherein 5-50% of amino acid sequences are added substituted and /or deleted in the disclosed SEQ ID NO:2 is not considered routine. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein 5-50% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to

teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed TIAP biological ctivity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed, since applicant has not presented enablement commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because it is unclear what is biological activity of the TIAP polypeptide that would be modulated by the interaction of a candidate compound with the TIAP polypeptide (which is 5-50% not-identical to human TIAP) in this context. For example the invention as claimed reads upon a chemical reaction in-vitro (compound and polypeptide) that results in the formation of compound-protein conjugates, which can be detected by an enzymatic reaction. On the other hand compound-protein interaction could be in the cellular micro

environment wherein such an interaction modulates a cascade of intracellular events involved in cellular physiology. It is unclear what is the biological activity modulated in this context.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

SUMESH KAUSHAL
PATENT EXAMINER